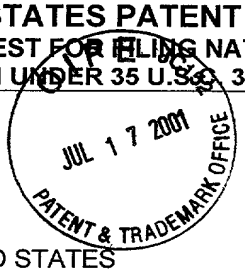
526 Rec'd PCT/PTO 17 JUL 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING NATIONAL PHASE OF PCT APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

09/889409

To: Hon. Commissioner of Patents
Washington, D.C. 20231



00909

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Atty Dkt: P 0281576 /Z 70474/UST
M# /Client Ref.

From: Pillsbury Winthrop LLP, IP Group:

Date: July 17, 2001

This is a **REQUEST** for **FILING** a PCT/USA National Phase Application based on:

1. International Application	2. International Filing Date	3. Earliest Priority Date Claimed
PCT/GB00/00280	1 February 2000	6 February 1999
⇧ country code	Day MONTH Year	Day MONTH Year (use item 2 if no earlier priority)

4. Measured from the earliest priority date in item 3, this PCT/USA National Phase Application Request is being filed within:

(a) ☐ 20 months from above item 3 date (b) ☒ 30 months from above item 3 date,

(c) Therefore, the due date (unextendable) is August 6, 2001

5. Title of Invention USE OF 3-HYDROXY-3-METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

6. Inventor(s) CAMERON, Norman Eugene et al

Applicant herewith submits the following under 35 U.S.C. 371 to effect filing:

7. ☒ Please immediately start national examination procedures (35 U.S.C. 371 (f)).

8. ☒ **A copy of the International Application** as filed (35 U.S.C. 371(c)(2)) is transmitted herewith (file if in English but, if in foreign language, file only if not transmitted to PTO by the International Bureau) including:

a. ☒ Request;
b. ☒ Abstract;
c. 21 pgs. Spec. and Claims;
d. _____ sheet(s) Drawing which are ☐ informal ☐ formal of size ☐ A4 ☐ 11"

9. ☒ **A copy of the International Application has been transmitted by the International Bureau.**

10. **A translation of the International Application** into English (35 U.S.C. 371(c)(2))

a. ☐ is transmitted herewith including: (1) ☐ Request; (2) ☐ Abstract;
(3) _____ pgs. Spec. and Claims;
(4) _____ sheet(s) Drawing which are:
☐ informal ☐ formal of size ☐ A4 ☐ 11"

b. ☐ is not required, as the application was filed in English.

c. ☐ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

d. ☐ Translation verification attached (not required now).

11. ☒ Please see the attached Preliminary Amendment

12. ☐ Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., before 18th month from first priority date above in item 3, are transmitted herewith (file only if in English) including:**

13. ☒ PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau

14. ☐ Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., of claim amendments** made before 18th month, **is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered canceled).**

15. **A declaration of the inventor** (35 U.S.C. 371(c)(4))
a. ☐ is submitted herewith ☐ Original ☐ Facsimile/Copy
b. ☒ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report (ISR):**
a. Was prepared by ☒ European Patent Office ☐ Japanese Patent Office ☐ Other
b. ☒ has been transmitted by the international Bureau to PTO.
c. ☒ copy herewith (1 pg(s).) ☒ plus Annex of family members (1 pg(s).).

17. **International Preliminary Examination Report** (IPER):
a. ☒ has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.
b. ☒ copy herewith in English.
c.1 ☐ IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:
c.2 ☐ Specification/claim pages #_____ claims #_____
Dwg Sheets #_____
d. ☐ Translation of Annex(es) to IPER **(required by 30th month due date, or else annexed amendments will be considered canceled).**

18. **Information Disclosure Statement** including:
a. ☒ Attached Form PTO-1449 listing documents
b. ☐ Attached copies of documents listed on Form PTO-1449
c. ☒ A concise explanation of relevance of ISR references is given in the ISR.

19. ☐ **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20. ☐ Copy of Power to IA agent.

21. ☐ **Drawings** (complete only if 8d or 10a(4) not completed): ___ sheet(s) per set: ☐ 1 set informal; ☐ Formal of size ☐ A4 ☐ 11"

22. Small Entity Status ☒ is **Not** claimed ☐ is claimed (**pre**-filing confirmation required)
22(a) _____ (No.) Small Entity Statement(s) enclosed (since 9/8/00 Small Entity Statements(s) not essential to make claim)

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) GREAT BRITAIN of:

	Application No.	Filing Date		Application No.	Filing Date
(1)	9902591.8	February 6, 1999	(2)	9902594.2	Sept. 6, 1999
(3)			(4)		
(5)			(6)		

a. ☒ See Form PCT/IB/304 sent to US/DO with copy of priority documents. If copy has not been received, please proceed promptly to obtain same from the IB.
b. ☐ Copy of Form PCT/IB/304 attached.

JC17 Rec'd PCT/PTO 17 JUL 2001

24. Attached: 2 copies of Form PCT/IB/306

25 Per Item 17.c2, **cancel original** pages #_____, claims #_____, Drawing Sheets #_____

26. **Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:**
Based on amended claim(s) per above item(s) ☐ 12, ☐ 14, ☐ 17, ☐ 25 (hilite)

Total Effective Claims	minus 20 =	x $18/$9	=	$0	966/967
Independent Claims	minus 3 =	x $80/$40	=	$0	964/965
If any proper (ignore improper) Multiple Dependent claim is present,		add$270/$135		+0	968/969

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)): →→ **BASIC FEE REQUIRED, NOW** →→→→

A. If country code letters in item 1 are **not** "US","BR","BB","TT","MX","IL" "NZ", "IN" or "ZA"

See item 16 re:

1.	Search Report was not prepared by EPO or JPO	add$1000/$500		960/961
2.	Search Report was prepared by EPO or JPO	add$860/$430	+860	970/971

SKIP B, C, D AND E UNLESS country code letters in item 1 are "US","BR","BB","TT","MX","IL", "NZ", "IN" or "ZA"

→ ☐	B. If USPTO did not issue both International Search Report (ISR) and (if box 4(b) above is X'd) the International Examination Report (IPER),	add$1000/$500	+0	960/961
(X) (only) (one) → ☐	C. If USPTO issued ISR but not IPER (or box 4(a) above is X'd),	add$710/$355	+0	958/959
(of) (these) (4) → ☐ (boxes)	D. If USPTO issued IPER but IPER Sec. V boxes not all 3 YES,	add$690/$345	+0	956/957
→ ☐	E. If international preliminary examination fee was paid to USPTO and Rules 492(a)(4) and 496(b) satisfied (IPER Sec. V all 3 boxes YES for all claims),	add $100/$50	+0	962/963
27		**SUBTOTAL =**	$860	
28	If Assignment box 19 above is X'd, add Assignment Recording fee of ----$40		+0	(581)
29.	Attached is a check to cover the	**TOTAL FEES**	$860	

Our Deposit Account No. 03-3975
Our Order No. 009901 (C#) | 0281576 (M#)

00909

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 and 492 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown above for which purpose a duplicate copy of this sheet is attached.
This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed

Pillsbury Winthrop LLP
Intellectual Property Group

By Atty: Donald J. Bird **Reg. No. 25323**

Sig:

Fax: (703) 905-2500
Tel: (703) 905-2018

Atty/Sec: DJB/mhn

NOTE: File in duplicate with 2 postcard receipts (PAT-103) & attachments.

#5.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of: Group Art Unit: To Be Assigned

CAMERON et al. Examiner: To Be Assigned

Appln. No.: 09/889,409

Filed: July 17, 2001

FOR: USE OF 3-HYDROXY-3-METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

Date: February 22, 2002

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Prior to taking up the subject application for a first action on the merits, please amend this application as follows:

IN THE CLAIMS:

Please cancel claims 1-21, without prejudice or abandonment of the subject matter thereof, and add the following new claims:

22. (New) A method for treating diabetic neuropathy in a warm blooded animal in need thereof comprising administering to said animal a treatment-effective amount of the statin drug (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

23. (New) A method for improving nerve conduction velocity or nerve blood flow in a warm blooded animal suffering diabetic neuropathy comprising administering to said animal a treatment-effective amount of the statin drug (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

24. (New) The method as claimed in claim 22 or 23 wherein the statin drug is administered as a pharmaceutical combination additionally comprising at least one other drug used for treating diabetes or the complications of diabetes.

25. (New) The method as claimed in claim 24 wherein the at least one other drug used for treating diabetes or the complications of diabetes is selected from insulin, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide, metformin, acarbose and repaglinide.

26. (New) The method as claimed in claim 23 wherein the statin drug is administered as a pharmaceutical combination additionally comprising a second drug which is also useful in improving nerve conduction velocity in a patient suffering diabetic neuropathy.

27. (New) The method as claimed in claim 26 wherein the second drug is selected from an aldose reductase inhibitor, an ACE inhibitor and an AII antagonist.

28. (New) The method as claimed in claim 27 wherein the second drug is selected from epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509), benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat,

trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, cilazapril, losartan, irbesartan, valsartan and candesartan.

29. (New) The method as claimed in claim 24 wherein the second drug is selected from an aldose reductase inhibitor, an ACE inhibitor and an AII antagonist.

30. (New) The method as claimed in claim 29 wherein the second drug is selected from epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509), benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, cilazapril, losartan, irbesartan, valsartan and candesartan.

31. (New) A pharmaceutical combination in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof; and lisinopril.

32. (New) A pharmaceutical combination in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof; and candesartan.

33. (New) A pharmaceutical combination in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid, or a pharmaceutically acceptable salt thereof; and
(S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid.

34. (New) A pharmaceutical composition in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]
(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof;
lisinopril; and
a pharmaceutically acceptable diluent or carrier.

35. (New) A pharmaceutical composition in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]
(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof;
candesartan; and
a pharmaceutically acceptable diluent or carrier.

36. (New) A pharmaceutical composition in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]
(3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof;
(S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, or 3-{4-
[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid; and
a pharmaceutically acceptable carrier or diluent.

37. (New) A method for the treatment of complications of diabetes in a warm blooded animal in need thereof comprising administering to said animal a treatment-effective amount of a pharmaceutical combination comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-
yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically aceptable salt thereof;
and
candesartan.

38. (New) A method for the treatment of complications of diabetes in a warm blooded animal in need thereof comprising administering to said animal a treatment-effective amount of a pharmaceutical combination comprising:

(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically aceptable salt thereof; and lisinopril.

39. (New) A method for the treatment of complications of diabetes in a warm blooded animal in need thereof comprising administering to said animal a treatment-effective amount of a pharmaceutical combination comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically aceptable salt thereof; and
(S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid.

40. (New) A pharmaceutical combination in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically aceptable salt thereof; and
an insulin sensitising agent.

41. (New) A pharmaceutical composition in unit dosage form comprising:
(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R, 5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically aceptable salt thereof;
an insulin sensitising agent; and
a pharmaceutically acceptable diluent or carrier.

REMARKS

Claims 1-21 have been cancelled and replaced by new claims 22-41. This amendment is being made at this time to focus the prosecution of this application on a particular embodiments of the originally disclosed and claimed invention, and without prejudice or waiver of applicant's right to prosecute the remaining subject matter of the original claims and specification in one or more continuing applications.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: February 22, 2002 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **009629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES

IN THE SPECIFICATION:

Claims 1-21 have been cancelled without prejudice or waiver.

New claims 22-41 have been added.

JC17 Rec'd PCT/PTO 17 JUL 2001
09/889409

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): CAMERON, Norman Eugene et al

Filed: Herewith

Title: USE OF 3-HYDROXY-3-METHYLGLUTARYL. . . .

July 17, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

☒ --This application is the National Phase of International Application PCT/GB00/00280 filed February 1, 2000 which designated the U.S. and that International Application

☒ was ☐ was not published under PCT Article 21(2) in English.--

Respectfully submitted,

PILLSBURY WINTHROP LLP
Intellectual Property Group

By: _____

Attorney: Donald J. Bird
Reg. No: 25323
Tel. No.: (202) 905-2018
Fax No.: (202) 905-2500

Atty\Sec. DJB/mhn
1600 Tysons Boulevard

McLean, VA 22102
(703) 905-2000

USE OF 3-HYDROXY-3-METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

The present invention relates to a new use of a statin drug in the improvement of diabetic neuropathy, specifically in improving nerve conduction velocity and nerve blood flow in patients suffering diabetes, in particular to pharmaceutical combinations of the statin drug and other agents known to improve diabetic neuropathy such as an aldose reductase inhibitor (ARI), an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II (AII) antagonist which combinations are useful in the prevention and treatment of the complications of diabetes.

3-Hydroxy-3-methylglutaryl Coenzyme A (HMG Co A) reductase inhibitors effectively inhibit cholesterol synthesis in the liver through stimulation of the low density lipoprotein (LDL) receptors. These drugs are currently pre-eminent in the treatment of all hypercholesterolaemia, except the relatively rarely occurring homozygous familial hypercholesterolaemia. Therapy with HMG Co A-reductase inhibitors may result in regression of atherosclerotic vascular lesions and several HMG Co A-reductase inhibitors have proven to reduce mortality. Various HMG Co A-reductase inhibitors are marketed, and are collectively referred to as 'statins'.

We have discovered that statin drugs, in particular (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the AGENT), the calcium salt of which is shown in Fig. 1 below, and atorvastatin produce an improvement in the nerve conduction velocity (NCV) and nerve blood flow in an animal model of diabetic neuropathy. Therefore, statin drugs may be used to improve diabetic neuropathy, whether in type I or type II diabetes.

Therefore we present as a first feature of the invention a method for treating neuropathy in a patient suffering from diabetes comprising administering to the patient a statin drug.

As a preferred feature of the invention we present a method for improving nerve conduction velocity and /or nerve blood flow in a patient suffering diabetic neuropathy comprising administering to the patient a statin drug.

Further features of the invention include use of a statin drug in the preparation of a medicament for use in the treatment of any of the conditions mentioned above.

Examples of statin drugs include, for example, pravastatin (PRAVACHOL™), lovastatin (MEVACOR™), simvastatin (ZOCOR™), cerivastatin (LIPOBAY™), fluvastatin (LESCOL™), atorvastatin (LIPITOR™) and the AGENT, the structures of which are shown in Figure 1. Preferably the statin drug is atorvastatin or the AGENT. Preferably the AGENT is used at a dose of 5 to 80 mg per day.

The AGENT is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase). Preferably the calcium salt is used as illustrated in Figure 1.

Atorvastatin is disclosed in US 5,273,995; lovastatin is disclosed in US 4,231,938; simvastatin is disclosed US 4,450,171 and US 4,346,227; pravastatin is disclosed in US 4,346,227; fluvastatin is disclosed in US 4,739,073; cerivastatin is disclosed in US 5,177,080 and US 5,006,530.

Other compounds which have inhibitory activity against HMG-CoA reductase can be readily identified by using assays well known in the art. Examples of such assays are disclosed in US 4,231,938 at column 6 and WO84/02131 at pages 30-33.

It will be appreciated that the statin drug may be administered in accordance with the invention in combination with other drugs used for treating diabetes or the complications of diabetes, such as neuropathy, nephropathy, retinopathy and cataracts. Examples of such treatments include insulin sensitising agents, insulin and oral hypoglycaemics (these are

divided into four classes of drug - sulfonylureas, biguanides, prandial glucose regulators and alpha-glucosidase inhibitors). Examples of insulin sensitising agents include, for example, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid. Examples of sulfonylureas are glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide. An example of a biguanide is metformin. An example of an alpha-glucosidase inhibitor is acarbose. An example of a prandial glucose regulator is repaglinide.

Other treatments are known also to improve NCV in diabetic neuropathy and as such these represent preferred combinations of the invention. Examples of such treatments include aldose reductase inhibitors, ACE inhibitors and AII antagonists.

The use of aldose reductase inhibitors or ACE inhibitors in improving NCV and treating diabetic neuropathy is disclosed in PCT/GB98/01959. The use of AII antagonists in improving NCV and treating diabetic neuropathy is disclosed in WO93/20816.

Suitable aldose reductase inhibitors include, for example, epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509).

Suitable ACE inhibitors include, for example, benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, and cilazapril. A preferred ACE inhibitor includes, for example, lisinopril, or a pharmaceutically acceptable salt thereof.

Suitable AII antagonists include, for example, losartan, irbesartan, valsartan and candesartan. A preferred AII antagonist is candesartan.

Independent aspects of the present invention include a pharmaceutical combination comprising any one of the statin drugs identified above, preferably the AGENT or atorvastatin, and any one of the named ACE inhibitors identified above, or anyone of the aldose reductase inhibitors identified above, or any one of the AII antagonists identified above. Accordingly, further independent aspects of the present invention include the following:

(1) A pharmaceutical combination comprising the AGENT and lisinopril;

(2) A pharmaceutical combination comprising atorvastatin and lisinopril;

(3) A pharmaceutical combination comprising fluvastatin and lisinopril;

(4) A pharmaceutical combination comprising pravastatin and lisinopril;

(5) A pharmaceutical combination comprising cerivastatin and lisinopril;

(6) A pharmaceutical combination comprising the AGENT and candesartan;

(7) A pharmaceutical combination comprising the AGENT, or atorvastatin, and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

The 'pharmaceutical combination' may be achieved by dosing each component drug of the combination to the patient separately in individual dosage forms administered together or sequentially. Alternatively the 'pharmaceutical combination' may be together in the same unit dosage form.

Therefore, as a further aspect of the invention we represent a pharmaceutical composition comprising a pharmaceutical combination as described herein above together with a pharmaceutically acceptable carrier and/or diluent.

Independent aspects of the present invention include a pharmaceutical composition comprising any one of the statin drugs identified above, preferably the AGENT or atorvastatin, and any one of the named ACE inhibitors identified above, or any one of the aldose reductase inhibitors identified above, or any one of the AII antagonists identified above together with a pharmaceutically acceptable carrier and/or diluent. Accordingly, further independent aspects of the present invention include the following:

(1) A pharmaceutical composition comprising the AGENT and lisinopril;

(2) A pharmaceutical composition comprising atorvastatin and lisinopril;

(3) A pharmaceutical composition comprising fluvastatin and lisinopril;

(4) A pharmaceutical composition comprising pravastatin and lisinopril;

(5) A pharmaceutical composition comprising cerivastatin and lisinopril;

(6) A pharmaceutical composition comprising AGENT and candesartan; and

(7) A pharmaceutical composition comprising the AGENT, or atorvastatin, and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid; and

together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT or atorvastatin and an ACE inhibitor (including any one of the ACE inhibitors specifically named above, in particular lisinopril), together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT or atorvastatin and an aldose reductase inhibitor (including any one specifically named above), together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT or atorvastatin and an AII antagonist (including any one specifically named above and preferably candesartan), together with a pharmaceutically acceptable carrier and/or diluent.

The pharmaceutical compositions of the present invention may be administered in a standard manner for example by oral or parenteral administration, using conventional systemic dosage forms, such as a tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, sterile injectable aqueous or oily solutions or suspensions. These dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like. In particular, compositions for oral administration are preferred.

The dose of a statin drug, an aldose reductase inhibitor, an AII antagonist or an ACE inhibitor which can be administered in accordance with the present invention depends on several factors, for example the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen and the desired result, and additionally the potency of the statin drug, aldose reductase inhibitor, AII antagonist and ACE inhibitor employed in the composition. In addition, account should be taken of the recommended maximum daily dosages for the ACE inhibitors.

Prolonged administration of an ACE inhibitor at a therapeutically effective dose may be deleterious or give rise to side effects in certain patients, for example it may lead to significant deterioration of renal function, induce hyperkalemia, neutropenia, angioneurotic oedema, rash or diarrhoea or give rise to a dry cough. Administration of an ARI may also give rise to deleterious effects or side effects at the dose required to inhibit the enzyme aldose reductase sufficiently to produce a significant beneficial therapeutic effect. The present invention lessens the problems associated with administration of an ARI or an ACE inhibitor alone

and/or provides a means for obtaining a therapeutic effect which is significantly greater than that otherwise obtainable with the single agents when administered alone. Furthermore, diabetic neuropathy involve a complex mechanism or number of mechanisms, which initiate a cascade of biochemical alterations that in turn lead to structural changes. These may result in a diverse patient population. The present invention therefore provides the additional advantage that it allows tailoring of treatment to the needs of a particular patient population.

The combination of a statin, preferably atorvastatin or the AGENT, with and ACE inhibitor, preferably lisinopril, is either additive or synergistic in effect in the treatment of neuropathy, in particular NCV or nerve blood flow, in diabetic pateients.

The combination of a statin, preferably atorvastatin or the AGENT, with and AII antagonist, preferably candesartan, is either additive or synergistic in effect in the treatment of neuropathy, in particular NCV or nerve blood flow, in diabetic pateients.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 100 mg of the statin drug, or/and from 0.1 mg to 500 mg of an aldose reductase inhibitor, or/and from 0.1 mg to 500 mg of an ACE inhibitor. Preferably a unit dose formulation will contain 5 to 80 mg of the statin drug, or/and 0.1 to 100 mg of an aldose reductase inhibitor, or/and 0.1 mg to 100 mg of an AII antagonist or/and 0.1 to 100 mg of an ACE inhibitor.

The present invention covers the pharmaceutical combination of (or product containing) the statin and an aldose reductase inhibitor, an AII antagonist or an ACE inhibitor for simultaneous, separate or sequential use in the treatment of diabetic neuropathy. In one aspect of the present invention, the AGENT drug and the aldose reductase inhibitor or AII antagonist or ACE inhibitor is presented in admixture in one pharmaceutical dosage form. In another aspect, the present invention covers the administration of separate unit dosages of the AGENT and aldose reductase inhibitor or AII antagonist or ACE inhibitor in order to achieve the desired therapeutic effect. Such separate unit dosages may be administered concurrently or sequentially as determined by the clinician. The present invention also covers an agent for

the treatment of diabetic neuropathy comprising a pharmaceutically acceptable carrier and/or diluent and, as active agents, a statin drug, preferably the AGENT or atorvastatin, and an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor in quantities producing a synergistic therapeutic effect.

In another aspect of the invention there is provided a combination of pharmaceutical compositions for combination therapy of diabetic neuropathy, the combination consisting of a pharmaceutical composition comprising the statin drug and a pharmaceutical composition comprising an aldose reductase inhibitor or a pharmaceutical composition comprising an AII antagonist or a pharmaceutical composition comprising an ACE inhibitor.

A further aspect of the present invention comprises the use of a statin drug and an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor in the preparation of a pharmaceutical composition for use in the treatment of diabetic neuropathy.

A further aspect of the present invention is a method for treating diabetic neuropathy wherein a therapeutically effective amount of a statin drug in combination with an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor is administered systemically, such as orally or parenterally. Where the patient to be treated is normotensive, the ACE inhibitor or AII antagonist will preferably be administered in amounts below that required to cause a reduction in blood pressure. Where the patient to be treated is hypertensive, the ACE inhibitor or AII antagonist will preferably be used in amounts usually employed to treat hypertension.

The effect of a pharmaceutical composition of the present invention may be examined by using one or more of the published models of diabetic neuropathy well known in the art. The pharmaceutical compositions of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, deficits in nerve function found in diabetic patients, and therefore particularly useful in the treatment of diabetic neuropathy. This may be demonstrated, for example, by measuring markers such as nerve conduction velocity, nerve blood flow, nerve evoked potential amplitude, quantitative sensory testing, autonomic function testing and morphometric changes. Experimentally, studies analogous to those

described in Diabetologia, 1992, Vol. 35, pages 12-18 and 1994, Vol. 37, pages 651-663 may be carried out.

A further aspect of the present invention is a method of treating or preventing the development of disease conditions associated with impaired neuronal conduction velocity in a warm-blooded animal (including a human being) requiring such treatment comprising administering to said animal a therapeutically effective amount of a pharmaceutical combination or composition as described above.

A further aspect of the present invention is a method of reversing impaired neuronal conduction velocity in a warm-blooded animal (including a human being) requiring such treatment comprising administering to said animal a therapeutically effective amount of a pharmaceutical combination or composition as described above.

Dosages of the AGENT may be administered according to the cholesterol lowering effect desired from a range of 5-80 mg per day in any number of unit dosages.

Suitable dosages of the statins, ACE inhibitors, aldose reductase inhibitors or AII antagonists mentioned herein are those which are available commercially, and which may be further reduced as suggested herein, or as advised in such publications as Monthly Index of Medical Specialities (P.O.BOX 43, Ruislip, Middlesex, UK).

The following non-limiting Examples serve to illustrate the present invention.

Example 1

Suitable pharmaceutical compositions of an aldose reductase inhibitor (ARI) include the following:

Tablet 1

	mg/tablet
ARI	100
Lactose Ph. Eur.	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

Tablet 2

ARI	50
Lactose Ph.Eur.	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

Tablet 3

ARI	1.0
Lactose Ph. Eur.	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

Capsule 1

ARI	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

Example 2

Suitable pharmaceutical compositions of an ACE inhibitor include the following:

Tablet 1

ACE Inhibitor	100
Corn starch	50
Gelatin	7.5
Microcrystalline cellulose	25
Magnesium stearate	2.5

Tablet 2

ACE inhibitor	20
Pregelatinised starch	82
Microcrystalline cellulose	82
Magnesium stearate	1

Example 3

Capsule	mg
The AGENT	5.0
Lactose	42.5
Corn starch	20.0
Microcrystalline cellulose	32.0
Pregelatinised starch	3.3
Hydrotalcite	1.1
Magnesium stearate	1.1

Capsules containing 1, 2.5 or 10mg of the Agent may be obtained similarly using more or less lactose as appropriate., to achieve a fill weight of 105mg.

Example 4

Suitable pharmaceutical compositions containing the AGENT and an ACE inhibitor in a single dosage form include the following:

Capsule	mg
The AGENT	5.0
Lisinopril	10.0
Lactose	42.5
Corn starch	20.0
Microcrystalline cellulose	32.0
Pregelatinised starch	3.3
Hydrotalcite	1.1
Magnesium stearate	1.1

Example 5

A patient requiring treatment for diabetic neuropathy is treated with the AGENT (10 mg) and lisinopril (10 mg). Lisinopril is administered twice daily and the AGENT is administered once daily.

Example 6

Male Sprague-Dawley rats, 19 weeks old at the start of the study, were divided into non-diabetic animals (normal control group) and animals rendered diabetic by intraperitoneal administration of streptozotocin, (40 - 45 mg/kg, freshly dissolved in sterile saline). Diabetes was verified 24 hours later by estimating hyperglycaemia and glucosuria (Visidex II and Diastix; Ames, Slough, UK). Diabetic rats were tested weekly and weighed daily. Animals were rejected if the plasma glucose concentration was < 20 mM of if body weight consistently increased over 3 days. Samples were taken from the tail vein or carotid artery after final experiments for plasma glucose determination (GOD-Perid method; Boehringer

Mannheim, Mannheim, Germany). After 6 weeks of untreated diabetes, groups of rats were treated for a further 2 weeks with the AGENT, dissolved in the drinking water.

At the end of the treatment period, rats were anaesthetised with thiobutabarbitone by intraperitoneal injection (50 - 100 mg/kg). The trachea was cannulated for artificial ventilation and a carotid cannula was used to monitor mean systemic blood pressure.

Motor nerve conduction velocity was measured (as previously described by Cameron et al, Diabetologia, 1993, Vol. 36, pages 299-304) between sciatic notch and knee in the nerve branch to tibialis anterior muscle, which is representative of the whole sciatic nerve in terms of susceptibility to diabetes and treatment effects.

Sensory conduction velocity in saphenous nerve was measured between the groin and ankle (as previously described by Cameron et al. Quarterly Journal of Experimental Physiology, 1989, vol. 74, pages 917-926).

Sciatic blood flow was measured by hydrogen clearance microelectrode polarography (as described by Cameron et al., Diabetologia, 1994, vol.37, pages 651-663). The nerve was exposed between the sciatic notch and the knee and the skin around the incision was sutured to a metal ring to form a pool that was filled with paraffin oil that was maintained at 35-37°C by radiant heat. A glass-insulated platinum micro-electrode was inserted into the middle portion of the sciatic nerve and polarised at 250mV with respect to a subcutaneous reference microelectrode. 10%Hydrogen was added to the inspired gas, the proportions of nitrogen and oxygen being adjusted to 70% and 20% respectively. When the hydrogen current recorded by the electrode had stabilised, indicating equilibrium with arterial blood, the hydrogen supply was shut off and nitrogen supply was increased appropriately. The hydrogen clearance curve was recorded until a baseline, defined as no systematic decline in electrode current over 5 minutes. To estimate blood flow , clearance curves were digitised and exponential curves were fitted to the data by computer using non-linear regression. The best fitting exponent gave a measure of nerve blood flow.

Data

All data expressed as group mean ± SEM (number of rats used in brackets)

Sciatic Nerve Motor Conduction Velocity

Control Values

Non-diabetical control	64.04 ± 0.46 (10)
8 week diabetic + vehicle	50.35 ± 0.93 (6)

Atorvastatin

9Diabetic + 2 weeks of dosing at 20mg/kg	61.53 ± 0.76 (6)
Diabetic + 2 weeks of dosing at 50mg/kg	63.59 ± 0.69 (6)

The AGENT

Diabetic + 2 weeks of dosing at 20mg/kg	63.34 ± 0.61 (8)

Dose response determination 5 groups of 8 rats - dose ranged from 0.3-20mg/kg - ED_{50} = 2.3mg/kg

Saphenous Nerve Sensory Conduction Velocity

Control Values

Non-diabetic control	61.09 m/s ± 0.67 (10)
8 week diabetic + vehicle	52.77 m/s ± 0.79 (6)

Atorvastatin

Diabetic + 2 weeks of dosing at 20mg/kg	59.77 m/s ± 0.93 (6)
Diabetic + 2 weeks of dosing at 50mg/kg	60.72 m/s ± 0.94 (6)

The AGENT

Diabetic + 2 weeks of dosing at 20mg/kg	60.57 m/s ± 0.83 (8)

Dose response determination 5 groups of 8 rats - dose ranged from 0.3-20mg/kg - ED_{50} = 0.9mg/kg

Sciatic Nerve Blood Flow

Control Values

Non-diabetic control	17.89 ml/min/100g (of nerve tissue) ± 0.65 (10)
8 week diabetic + vehicle	8.82 ml/min/100g ± 0.56 (10)

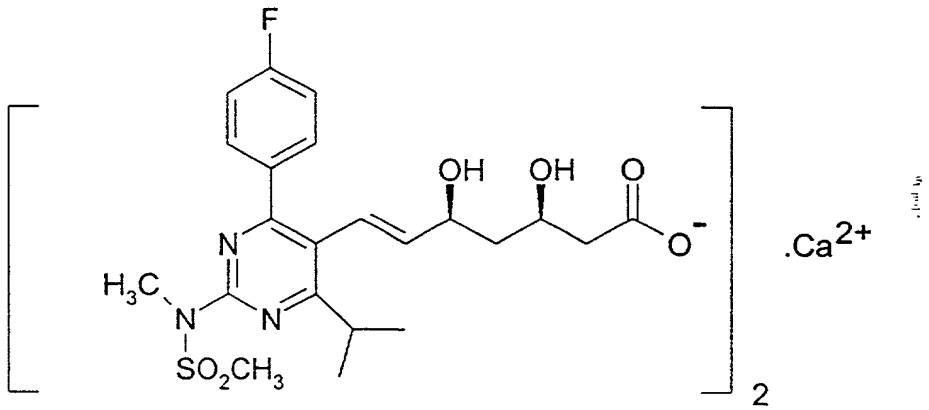
Atorvastatin

Diabetic + 2 weeks of dosing at 50mg/kg	16.96 ± 1.39 ml/min/100g (6)

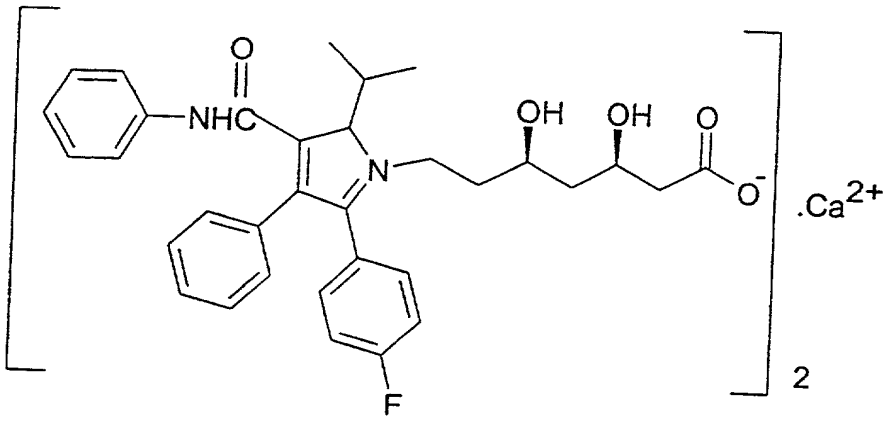
The AGENT

Diabetic + 2 weeks of dosing at 20mg/kg	16.19 ± 0.51 ml/min/100g (8)

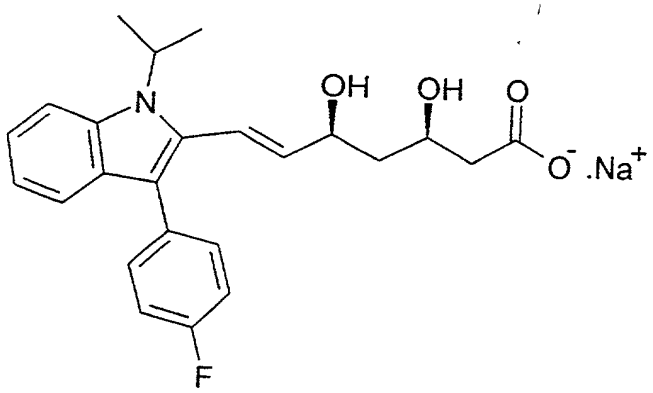
Figure 1.



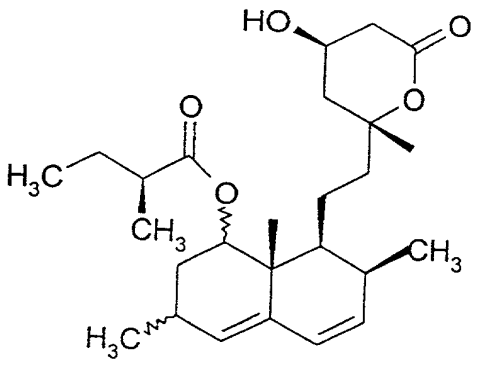
The AGENT



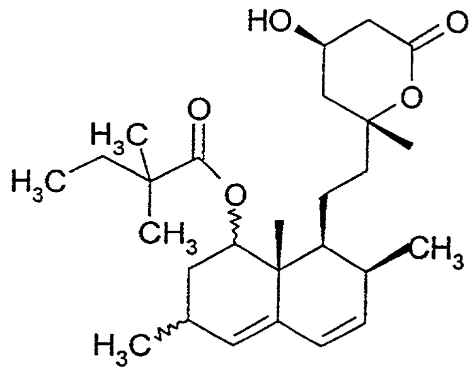
Atorvastatin



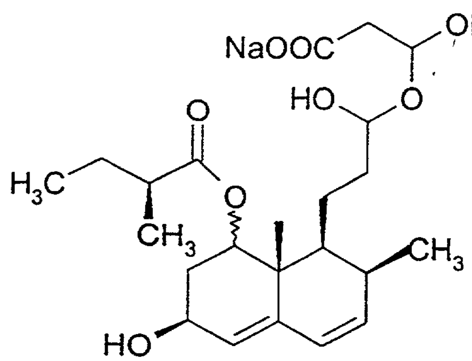
Fluvastatin



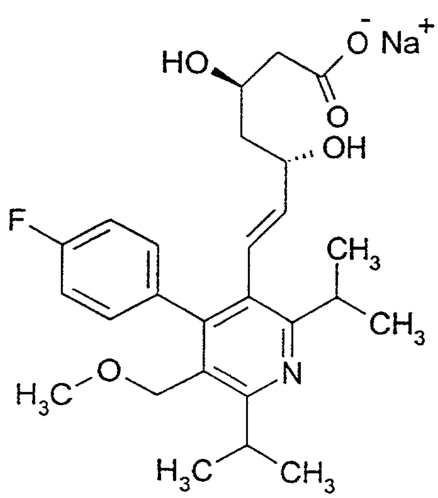
Lovastatin



Simvastatin



Pravastatin



Cerivastatin

Claims

1. A method for treating neuropathy in patients suffering from diabetes comprising administering to the patient a statin drug.

2. A method for improving nerve conduction velocity or nerve blood flow in a patient suffering diabetic neuropathy comprising administering to the patient a statin drug.

3. Use of a statin drug in the preparation of a medicament for use in the treatment of diabetic neuropathy.

4. Use of a statin drug in the preparation of a medicament for use in the improvement of nerve conduction velocity or nerve blood flow in a patient having diabetic neuropathy.

5. A method as claimed in either claim 1 or claim 2 wherein the statin drug is selected from pravastatin, simvastatin, cerivastatin, fluvastatin, atorvastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

6. Use as claimed in either claim 3 or claim 4 wherein the statin drug is selected from pravastatin, simvastatin, cerivastatin, fluvastatin, atorvastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

7. A method as claimed in claim 1, 2 or 5 wherein the statin drug is used in combination with at least one other drug used for treating diabetes or the complications of diabetes.

8. A method as claimed in claim 7 wherein the drug used for treating diabetes or the complications of diabetes is selected from insulin, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic

acid, glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide, metformin, acarbose and repaglinide.

9. Use as claimed in claim 3, 4 or 6 wherein the statin drug is used in combination with at least one other drug used for treating diabetes or the complications of diabetes.

10. Use as claimed in claim 9 wherein the drug used for treating diabetes or the complications of diabetes is selected from insulin, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide, metformin, acarbose and repaglinide.

11. A method as claimed in claim 2 or 5 wherein the statin drug is used in combination with a second drug which is also useful in improving nerve conduction velocity in a patient suffering diabetic neuropathy.

12. A method as claimed in claim 11 wherein the second drug is selected from an aldose reductase inhibitor, an ACE inhibitors and an AII antagonist.

13. A method as claimed in claim 12 wherein the second drug is selected from epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509), benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, cilazapril, losartan, irbesartan, valsartan and candesartan.

14. Use as claimed in either claim 3 or 6 wherein the statin drug is used in combination with a second drug which is also useful in improving nerve conduction velocity in a patient suffering diabetic neuropathy.

15. A method as claimed in claim 14 wherein the second drug is selected from an aldose reductase inhibitor, an ACE inhibitors and an AII antagonist.

16. A method as claimed in claim 15 wherein the second drug is selected from epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509), benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, cilazapril, losartan, irbesartan, valsartan and candesartan.

17. A pharmaceutical combination comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and lisinopril.

18. A pharmaceutical combination comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and candesartan.

19. A pharmaceutical combination comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, or atorvastatin, and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

20. A pharmaceutical composition comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, lisinopril and a pharmaceutically acceptable diluent or carrier.

21. A pharmaceutical composition comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, or atorvastatin, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, and a pharmaceutically acceptable carrier or diluent.

FOR UTILITY/DESIGN
CIP/IPCT NATIONAL/PLANT
ORIGINAL/SUBSTITUTE/SUPPLEMENTAL
DECLARATIONS

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PW
FORM
Z70474/UST

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the **INVENTION ENTITLED:** USE OF 3-HYDROXY-3-METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

the specification of which (CHECK applicable BOX(ES))
X BOX(ES) A. ☐ is attached hereto.
→ B. ☐ was filed on _____ as U.S. Application No._____
→ → C. ☐ was filed as PCT International Application No. PCT/ GB00/00280 on 01 February 2000
and (if applicable to U.S. or PCT application) was amended on _____ I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F R. 1 56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 1 19(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first laid-open or Published	Date Patented or Granted	Priority NOT Claimed
9902591.8	United Kingdom	6.02.1999			
9902594.2	United Kingdom	06.02.1999			

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NON PROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status Pending, abandoned, patented	Priority NOT Claimed

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 16 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Winthrop LLP, Intellectual Property Group, telephone number (202)861-3000 (to whom all communications are to be directed), and persons of that firm who are associated with USPTO Customer No.909 (see below label) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete from that Customer No. names of persons no longer with their firm, to add new persons of their Firm to that Customer No., and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or an attorney of that Firm in writing to the contrary.

00909

(1) INVENTOR'S SIGNATURE Norman E. Cameron **Date:** 11 July 2001

Name 1-00	NORMAN	E.	CAMERON
	First	Middle Initial	Family Name
Residence	A		RAZA
	Aberdeen GBX		United Kingdom
	City	State/Foreign Country	Country of Citizenship
Mailing Address	Institute of Medical Sciences, Diabetic Complications Laboratory, Foresterhill, Aberdeen, AB25 2ZD, United Kingdom		
(include Zip Code)			

(2) INVENTOR'S SIGNATURE Mary Cotter **Date:** 11 July 2001

Name 2-00	MARY	A.	COTTER
	First	Middle Initial	Family Name
Residence	Aberdeen GBX		United Kingdom
	City	State/Foreign Country	Country of Citizenship
Mailing Address	Institute of Medical Sciences, Diabetic Complications Laboratory, Foresterhill, Aberdeen, AB25 2ZD, United Kingdom		
(include Zip Code)			

☐ OR ADDITIONAL INVENTORS see attached page.
☐ See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. P_____
(M#)

DECLARATION AND POWER OF ATTORNEY
(continued)